Short Communication

A *de novo* duplication of chromosome 21q22.11 → qter associated with Down syndrome: Prenatal diagnosis, molecular cytogenetic characterization and fetal ultrasound findings

Chih-Ping Chen a,b,c,d,e,f,1,*, Hsu-Kuang Huang g,1, Pei-Ying Ling g, Yi-Ning Su h, Ming Chen i,j,k,l, Fuu-Jen Tsai d,m,n, Pei-Chen Wu a, Schu-Rern Chern b, Yu-Ting Chen b, Chen-Chi Lee a, Wayseen Wang b,o

a Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Taipei, Taiwan
b Department of Medical Research, Mackay Memorial Hospital, Taipei, Taiwan
c Department of Biotechnology, Asia University, Taichung, Taiwan
d School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan
e Institute of Clinical and Community Health Nursing, National Yang-Ming University, Taipei, Taiwan
f Department of Obstetrics and Gynecology, School of Medicine, National Yang-Ming University, Taipei, Taiwan
1 Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Taipei, Taiwan
h Department of Obstetrics and Gynecology, Taiwan Adventist Hospital, Taipei, Taiwan
i Department of Medical Research, National Taiwan University Hospital, Taipei, Taiwan
j Department of Medical Genetics, National Taiwan University Hospital, Taipei, Taiwan
k Department of Genetics, Changhua Christian Hospital, Changhua, Taiwan
l Department of Obstetrics and Gynecology, Changhua Christian Hospital, Changhua, Taiwan
m Department of Medical Research, Changhua Christian Hospital, Changhua, Taiwan
n Department of Obstetrics and Gynecology, College of Medicine, National Taiwan University, Taipei, Taiwan
o Department of Medical Research, China Medical University Hospital, Taichung, Taiwan

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Abstract

**Objectives:** To present prenatal diagnosis and molecular cytogenetic characterization of *de novo* partial partial trisomy 21q (21q22.11 → qter) associated with clinodactyly and hypoplastic midphalanx of the fifth fingers, midface hypoplasia, and an intracardiac echogenic focus on prenatal ultrasound.

**Materials, Methods, and Results:** A 34-year-old gravida 2, para 1 woman underwent amniocentesis at 20 weeks of gestation because of fetal structural abnormalities on prenatal ultrasound. A level II ultrasound at 20 weeks of gestation showed polyhydramnios, clinodactyly and hypoplastic midphalanx of the fifth fingers, midface hypoplasia, and an intracardiac echogenic focus. Amniocentesis revealed an aberrant derivative chromosome 9, or der(9). Parental karyotypes were normal. Spectral karyotyping (SKY) and fluorescence *in situ* hybridization (FISH) analyses revealed that the der(9) contained a segment of chromosome 21 distal to chromosome 9q, and FISH analysis additionally showed that the distal subtelomeric region of 9q was not deleted. Array comparative genomic hybridization (aCGH) demonstrated a 14.8-Mb duplication of distal 21q encompassing the Down syndrome critical region (DSCR) but no genomic imbalance in the distal euchromatic region of chromosome 9. The karyotype was 46,XX,der(9)(q34.3;q22.11)dn. Polymorphic DNA marker analysis revealed the maternal origin of the aberrant chromosome. The pregnancy was subsequently terminated. A malformed female fetus was delivered with a characteristic phenotype of Down syndrome.

**Conclusion:** SKY, FISH and aCGH are useful in prenatal investigation of the nature of a *de novo* aberrant derivative chromosome. Partial trisomy 21q encompassing the DSCR may present characteristic Down syndrome features on prenatal ultrasound.

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**Keywords:** 21q22; 21q duplication; Down syndrome; Partial trisomy 21q; Prenatal diagnosis; Ultrasound
Introduction

Prenatal diagnosis of a de novo unbalanced translocation may require molecular cytogenetic technologies, such as fluorescence in situ hybridization (FISH), spectral karyotyping (SKY) and array-based comparative genomic hybridization (aCGH) to identify the nature of the de novo derivative chromosome. We previously reported the usefulness of FISH, SKY and aCGH in the identification of a de novo derivative chromosome derived from an unbalanced translocation [1,2].

Fig. 1. Prenatal ultrasound at 20 weeks of gestation shows (A) midface hypoplasia, (B) clinodactyly of the fifth finger with hypoplasia of midphalanx (arrow) and (C) an intracardiac echogenic focus (arrow).

Fig. 2. G-banded karyotype shows a derivative chromosome 9, or der(9). The proband’s karyotype is 46,XX,der(9)t(9;21)(q34.3;q22.11)dn.
Here, we additionally report prenatal diagnosis and molecular cytogenetic characterization of \textit{de novo} partial trisomy 21q (21q22.11 → qter) derived from an unbalanced translocation associated with some of features of Down syndrome, such as clinodactyly and hypoplastic midphalanx of the fifth fingers, midface hypoplasia and an intracardiac echogenic focus on prenatal ultrasound.

\textbf{Materials, methods and results}

A 34-year-old gravida 2, para 1 woman was suggested to undergo amniocentesis at 18 weeks of gestation because of advanced maternal age, but she declined. Her husband was aged 34 years. She had a 2½-year-old healthy daughter. A level II ultrasound at 20 weeks of gestation showed polyhydramnios and some of the features of Down syndrome, such as clinodactyly and hypoplastic midphalanx of the fifth fingers, midface hypoplasia, and an intracardiac echogenic focus (Fig. 1). The woman decided to undergo amniocentesis. Amniocentesis revealed an aberrant derivative chromosome 9, or der(9) (Fig. 2). Chromosome preparations of the blood lymphocytes from the parents revealed normal karyotypes. The derivative chromosome was characterized by SKY using 24-color SKY probes (Applied Spectral Imaging, Carlsbad, CA, USA) and by FISH using DNA probe mixtures containing the 9q and 21q subtelomeric probes. The SKY analysis revealed that the der(9) contained a segment of chromosome 21 in the distal end of the long arm of a chromosome 9 (Fig. 3). The FISH analysis showed that the chromosome 21 segment in the distal end of the long arm of der(9) was of 21q in origin, and the distal subtelomeric region of 9q was not deleted (Fig. 4). Bacterial artificial chromosome (BAC)-based aCGH [CMDX BAC-based aCGH CA3000 chips (CMDX, Irvine, CA, USA)] further demonstrated a 14.8-Mb duplication of distal 21q \texttt{[arr cgh 21q22.11q22.3 (32,110,552–46,944,323)×3]} (NCBI build 36, March 2006) (Fig. 6). Whole genome analysis by aCGH revealed no genomic imbalance in the distal euchromatic region of chromosome 9 (Fig. 6). The karyotype was 46,XX,der(9)t(9;21)(q34.3;q22.11)dn (Fig. 2). Polymorphic DNA marker analysis revealed the maternal origin of the aberrant chromosome. The parents opted to terminate the pregnancy.
pregnancy. A malformed female fetus was delivered with a flat facial profile, hypertelorism, low-set ears, a depressed nasal bridge, clinodactyly, hypoplastic midphalanx of the fifth fingers, brachycephaly and epicanthic folds (Fig. 7).

Discussion

We have presented prenatal sonographic and molecular cytogenetic characterization of a second-trimester fetus with some clinical features of Down syndrome resulting from a pure partial trisomy 21q (21q22.11→qter) due to a de novo unbalanced translocation. Down syndrome with an unbalanced translocation involving a duplication of the Down syndrome critical region (DSCR) is very rare and accounts for less than 1% of the cases with Down syndrome [3]. DSCR is the critical region on chromosome 21 on which the duplication will be sufficient to cause the Down syndrome phenotype. DSCR has been narrowed down to 21q22 with an approximate length of 5.4 Mb within 21q22.1-q22.3 [4,5]. Ronan et al. [6] additionally reported a 4.3-Mb region within 21q22.13-q22.2 with typical facial features of Down syndrome but no congenital heart defects. Recently, Eggermann et al. [7] narrowed down the DSCR in 21q22 with a 0.46-Mb duplication in 21q22 affecting the KCNE1 and DSCR1/RCAN1 genes.

To date, at least 38 cases of Down syndrome with pure partial trisomy 21 have been reported [3,6–23]. Our case manifested some of the clinical features of Down syndrome similar to the cases reported by Nadal et al. [20] and Vaglio et al. [23]. Nadal et al. [20] reported a 2-year-11-month-old boy with pure partial trisomy 21q (21q22.1→qter) due to an intrachromosomal duplication, short stature, brachycephaly, a flat face, oblique palpebral fissures, epicanthic folds, a flat nasal bridge, a high palate, malformed and low-set ears, short and broad hands with clinodactyly of the fifth fingers, moderate mental retardation and delayed psychomotor development. Vaglio et al. [23] reported a 4-year-10-month-old girl with pure partial trisomy 21q (21q22.1→qter) due to a de novo intrachromosomal duplication, a flat broad face,
brachycephaly, a flat nasal bridge, upwardly slanted palpebral fissures, epicanthic folds, blepharitis, brushfield spots, strabismus, a wide mouth with downturned corners, a prominent low lip, a narrow tongue and a short palate, but the diagnostic criteria for mental retardation were not fulfilled.

The present case manifested clinodactyly, midface hypoplasia, an intracardiac echogenic focus and hypoplastic midphalanx of the fifth fingers on prenatal ultrasound. Prenatal diagnosis of pure partial trisomy 21q associated with Down syndrome is very rare. Lee et al. [22] reported prenatal diagnosis

Fig. 6. Oligonucleotide-based aCGH shows (A) a 14.8-Mb distal 21q duplication [arr cgh 21q22.11q22.3 (32,110,552–46,944,323) ×3], and (B) no genomic imbalance in the distal euchromatic region of chromosome 9q.
of pure trisomy 21q (21q13 → q22.2) due to an unbalanced cryptic insertion (4;21)(q21;q22.1q22.3) inherited from the carrier father. The mother was aged 32 years. The fetus had a karyotype of 46,XX,der(4)ins(4;21)(q21;q22.13q22.2)pat. The abnormal prenatal findings included a maternal serum screening Down syndrome risk of 1:17 and a thick nuchal fold. The fetus was delivered with clinical features of Down syndrome. Ronan et al. [6] reported prenatal diagnosis of bilateral septated cystic hygroma and hydrops in a fetus with pure trisomy 21q (21q22.13 → q22.2) due to a 4.3-Mb intrachromosomal duplication of 21q22.13-q22.2 inherited from the mother who had the facial gestalt of Down syndrome. Chorionic villus sampling (CVS) at 12 weeks of gestation failed to identify the subtle chromosome abnormalities. Postnatal reexamination of the CVS samples using FISH showed a microduplication of 21q22.13-q22.2 on one chromosome 21. The maternal DNA study using aCGH revealed a 4.3-Mb gain of one copy of the same region.

The present case had a duplication of 21q22.11-qter encompassing some genes associated with the pathophysiology of Down syndrome such as DSCR1 (OMIM 602917), DSCR2 (OMIM 605296), DSCR3 (OMIM 605298), DSCR4 (OMIM 604829), DSCR6 (OMIM 609892), DSCR8 or MMA1 (OMIM 613396), DSCR10, SIM2 (OMIM 600892) and Dyrk1a (OMIM 600855). DSCR1 or Rcan1 (regulator of calcineurin 1) (gene map at 21q22.11-q22.2) protein is overexpressed in the brain of the fetuses with Down syndrome. DSCR1 protein interacts with calcineurin A, and overexpression of DSCR1 will inhibit calcineurin-dependent gene transcription through the inhibition of NFAT (OMIM 600489) signaling pathway [24]. Ermak et al. [25] suggested that overexpression of DSCR1 will inhibit calcineurin activity and causes accumulation of hyperphosphorylated tau protein and production of neurofibrillary tangles causing Alzheimer’s disease. Dyrk1a (dual-specificity tyrosine phosphorylation-regulated kinase 1A) (gene map at 21q22.1) has been suggested to be involved in the abnormal neurogenesis found in Down syndrome [26]. Arron et al. [5] suggested that in Down syndrome, with a 1.5-fold increase in the gene dosage within Dscr1, Dscr1 and Dyrk1a will cooperatively destabilize the NFAT genetic regulatory circuit, leading to NFAT dysregulation and abnormal phenotypes in Down syndrome. Sim2 (homolog of Drosophila single-minded 2) gene plays an important role in Drosophila development and encodes a basic helix-loop-helix protein that is a transcription factor in the midline development of CNS. Chen et al. [27] suggested that human Sim gene is a candidate for facial and skull dysmorphology, brain abnormalities and mental retardation of Down syndrome. In the mouse model, overexpression of sim2 gene contributes to the pathogenesis of Down syndrome [28,29].

In conclusion, aCGH is useful for rapid identification of the genomic imbalance associated with a de novo derivative chromosome, and SKY, FISH and aCGH are useful in prenatal investigation of the nature of a de novo aberrant derivative chromosome. Partial trisomy 21q encompassing the DSCR may present characteristic Down syndrome features on prenatal ultrasound.

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References


Fig. 7. (A) Craniofacial profile and (B) the abnormal fifth finger with hypoplastic midphalanx (arrow) at birth.


